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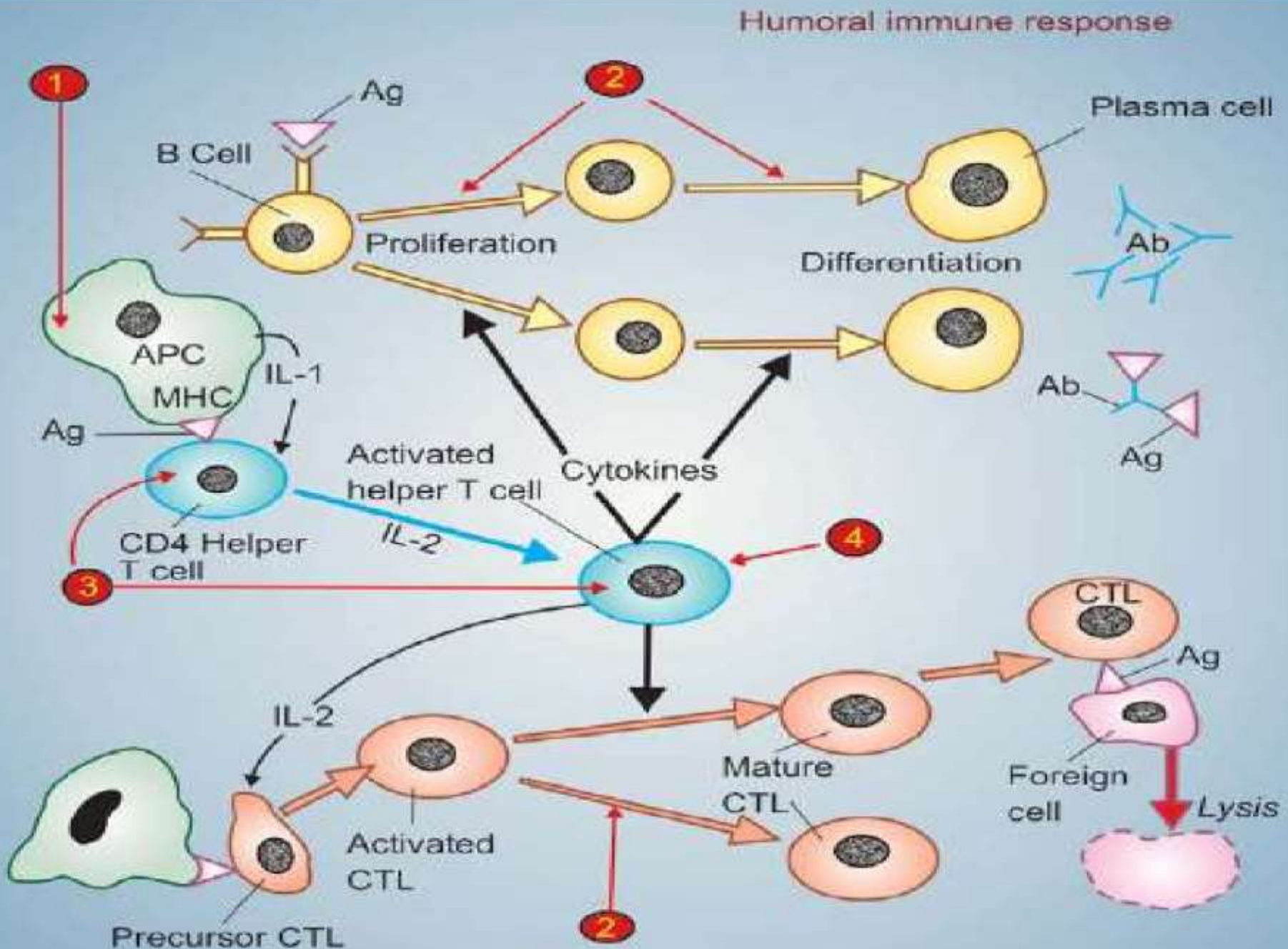
Department: Pharmacy
Subject: Pharmacology-III (BP 602T)
Unit: IV
Topic: Pharmacology of Immunosupressants

Introduction

- Immunosuppressant drugs inhibit cellular/ humoral or both immune response and have their major use in organ transplantation and auto immune diseases.
- These drugs have met a high degree of success in organ transplant and autoimmune diseases.
- However, such therapies require life time use and non specifically suppresses the entire immune system

- A narrow therapeutic index.
- Therapeutic monitoring plays a key role in maintaining plasma n blood levels of thedrug.
- Variation in concentration outside narrow therapeutic range can result in adverse effects.
- Concentrations are not too high or low, there by reducing the risks of toxicity or rejection.


Humoral immune response
1
Ag
2
Plasma cell
B Cell
Proliferation
Differentiation
Ab
APC
MHC
IL-1
Ab
Ag
Ag
Activated
helper T cell
Cytokines
CD4 Helper
T cell
IL-2
3
4
CTL
Ag
IL-2
Mature
CTL
Foreign
cell
Lysis
Activated
CTL
Precursor CTL
2
Cell mediated immune response

IMMUNOSUPPRESSANT DRUGS

CALCINEURIN INHIBITORS

- Cyclosporine, Tacrolimus

m. TOR INHIBITORS

- Sirolimus, Everolimus

ANTIPROLIFERATIVE DRUGS

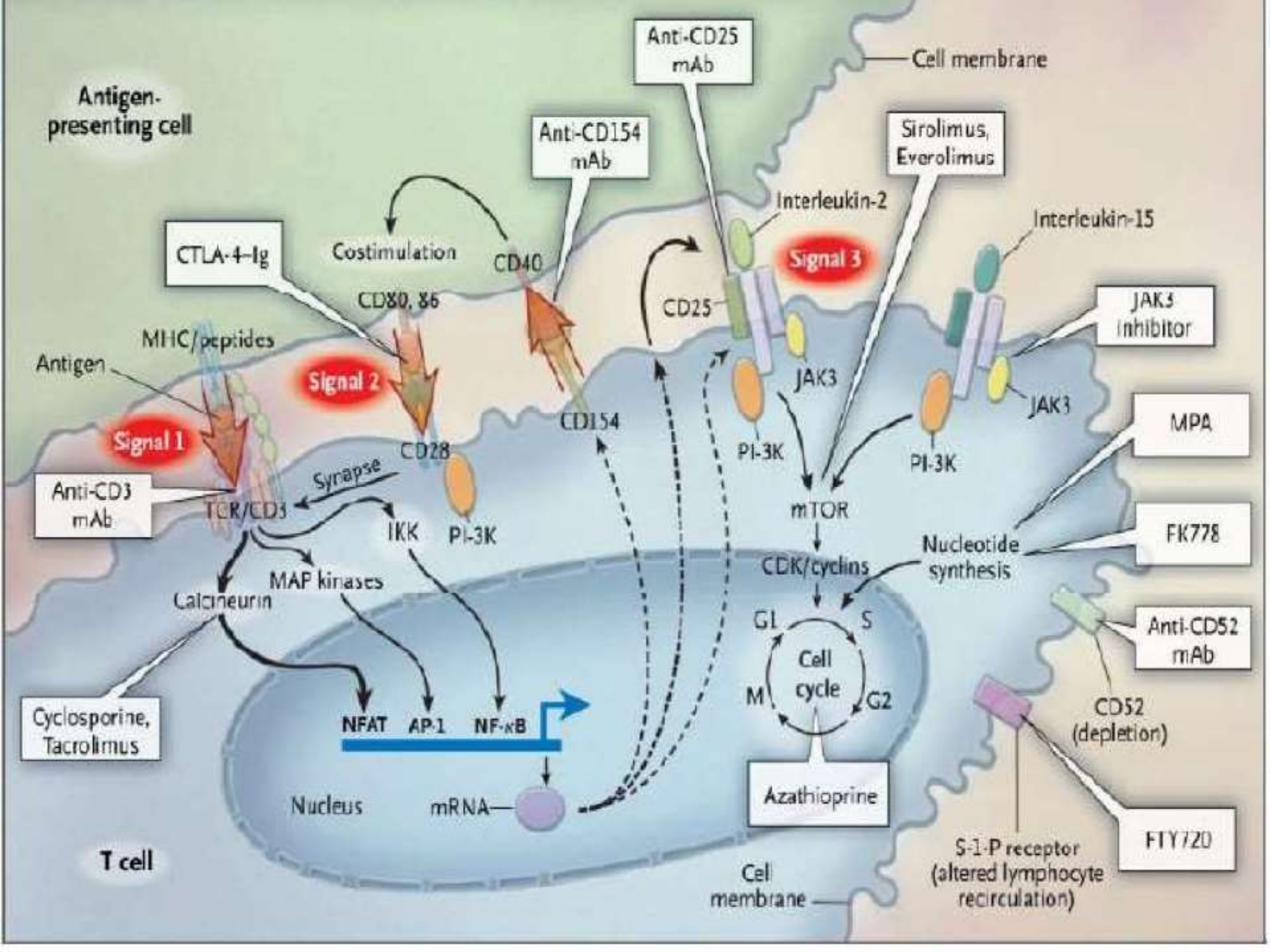
- Azathioprine, Methotrexate, Cyclophosphamide, Chlorambucil, Mycophenolate mofetil.

GLUCOCORTICOIDS

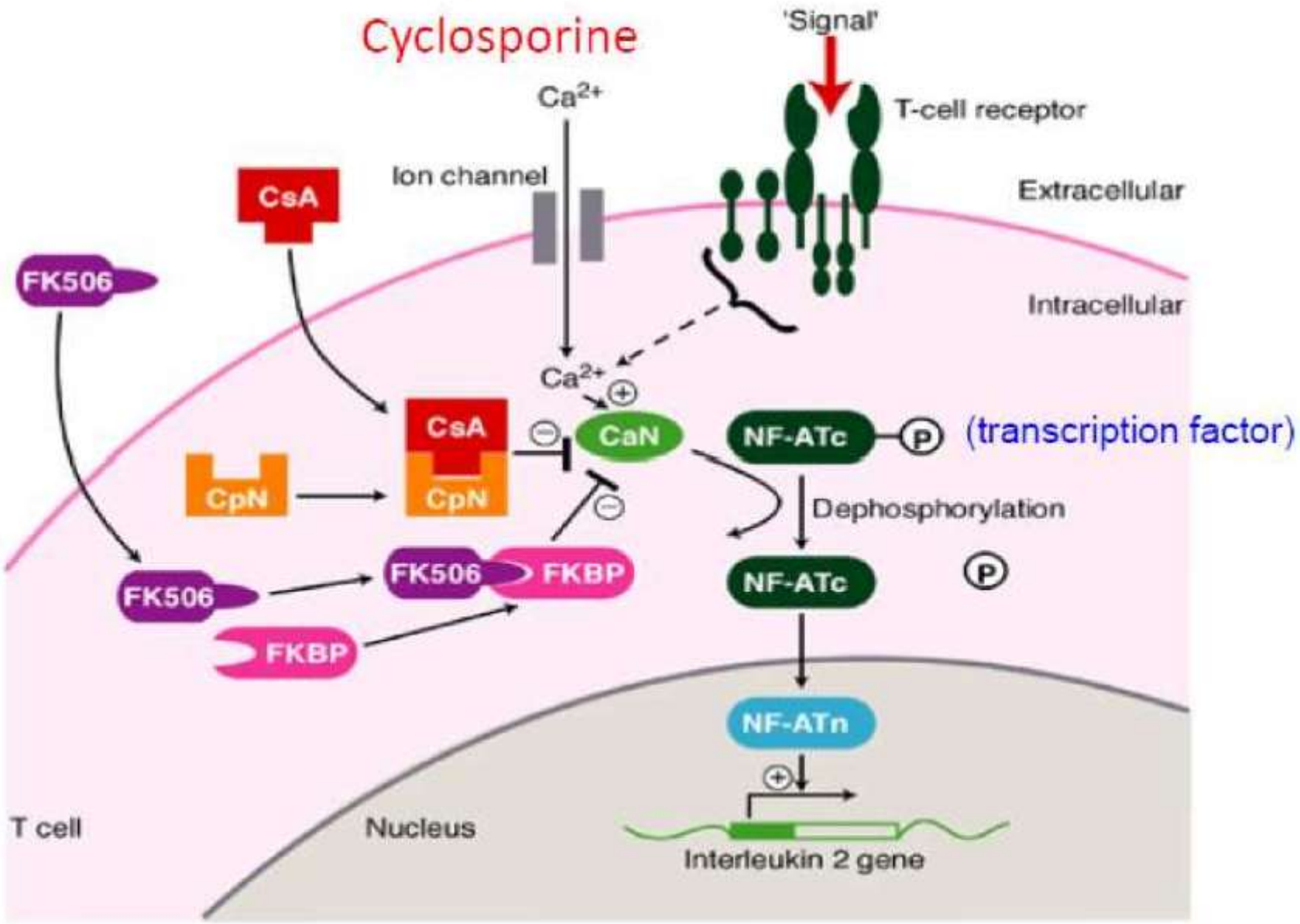
- Prednisolone

BIOLOGICAL AGENTS

- TNFα Inhibitors:- Infliximab, Adalimumab
- IL-1 Receptor antagonist:- Anakinra
- IL-2 Receptor antagonist:- Daclizumab, Basiliximab
- Antibodies:- Muromonab CD3

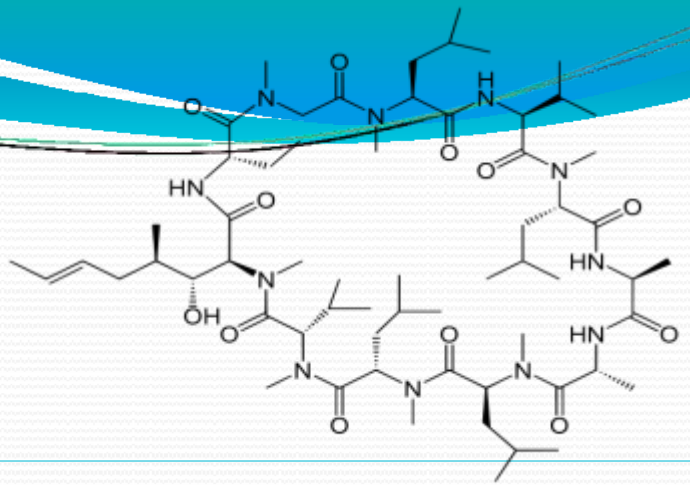

Antigen-presenting cell
Ant-CD25 mAb
Cell membrane
Anti-CD154 mAb
Sirolimus, Everolimus
Interleukin-2
Interleukin-15
CTLA-4-Ig
Costimulation
CD40
Signal 3
CD80, 86
CD25
JAK3 Inhibitor
MHC/peptides
Antigen
Signal 2
JAK3
JAK3
CD154
MPA
Signal 1
CD28
PI-3K
PI-3K
Anti-CD3 mAb
Synapse
TCR/CD3
IKK
PI-3K
mTOR
FK778
Nucleotide synthesis
CDK/cyclins
MAP kinases
Calcineurin
G1
S
Anti-CD52 mAb
Cell cycle
M
G2
Cyclosporine, Tacrolimus
NFAT
AP-1
NF-κB
CD52 (depletion)
Azathioprine
Nucleus
mRNA
FTY720
T cell
S-1-P receptor (altered lymphocyte recirculation)
Cel membrane

CALCINEURIN INHIBITORS



Mechanism of action of cyclosporine or tacrolimus (FK506)

CYCLOSPORINE



- *Cyclosporine is a cyclic polypeptide with 11 amino acids, derived from fungus* ***Tolypocladium inflatum.***
- *Cyclosporine is a specific inhibitor of T-cell mediated immunity which enabled whole-organ transplantation.*
- *It sis used to prevent rejection of kidney, liver, and cardiac allogeneic transplants.*
- *Cyclosporin does not affect nonspecific functions like phagocytosis and metabolism of foreign substances.*

Pharmacokinetics:-

- It is effective by both oral and IV route.
- It is metabolixed by microsomal enzymecytochrome P450 in the liver.
- Excretion of the metabolites is through the biliary route, with only a small fraction of the parent drug appearing in the urine.
- Plasma half-life is 27 hrs.

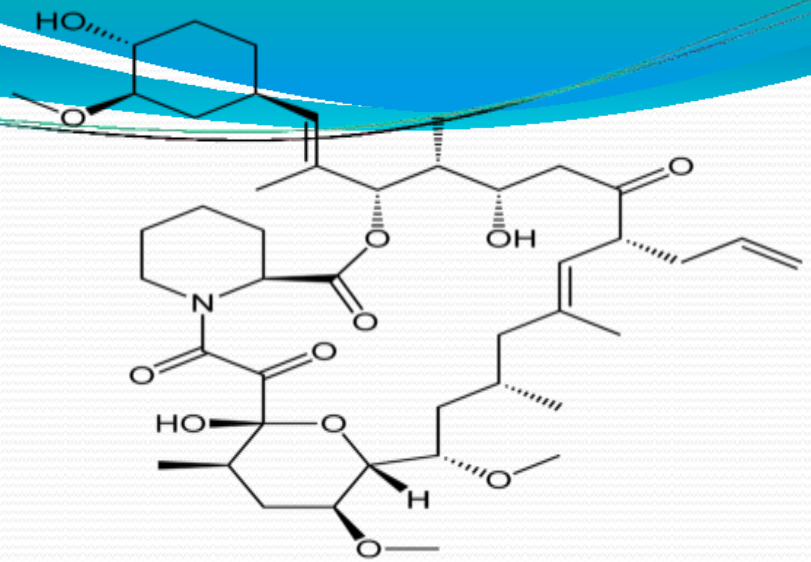
ADVERSE EFFECTS:-

- *Nephrotoxicity*
- *Hepatotoxicity*
- *Anorexia*
- *Gum hypertrophy*
- *Hypertension*
- *Hyperlipidemia*
- *Hirsutism*
- *Osteoporosis*
- *Tremor*
- *Seizures*

Uses:-

- In organ transplantation:- Kidney, liver, bone marrow, and other transplants.
- Autoimmune disorders:- severe psoriasis, uveitis, atopic dermatitis, inflammatory bowel disease and nephrotic syndrome.
- In treatment of asthma.
- Rheumatoid arthritis.
- Early treatment of type-1 diabetes.
- Prevention and treatment of graft rejection reactions.

TACROLIMUS



- *Tacrolimus , originally called FK506.*
- *It is a macrolide derived from soil fungus Streptomyces tsukabaensis.*
- *It is generally 50-100 times more potent than cyclosporine.*
- *Use:-*

  For prevention and graft rejection in organ transplantation similar to cyclosporine.

Pharmacokinetics:-

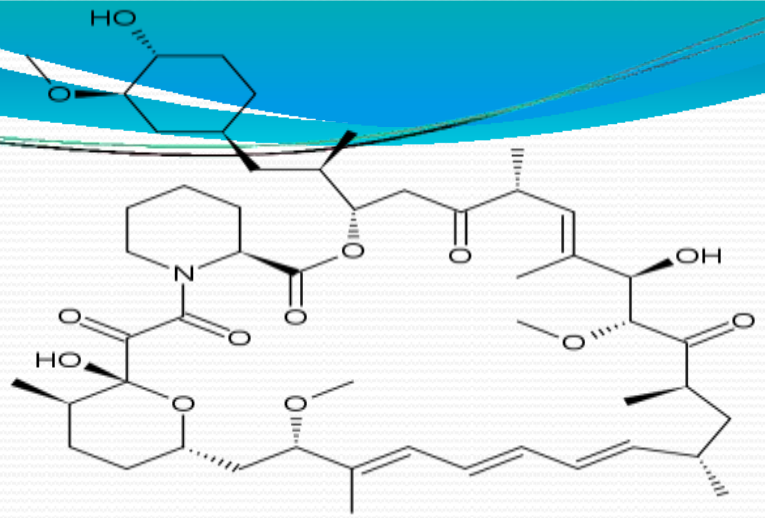
- It can be given orally or intravenously.
  Absorption is decreased if the drug is taken with high-fat meals.
- Highly bound to serum proteins and concentrated inerythrocytes.
- Metabolized by cytochrome P-450 enzyme.
- Excreated in bile.
- Half-life of 12hr.

ADVERSE EFFECTS:-

- *Nephrotoxicity.*
- *Gastrointestinal disturbances.*
- *Hypertension.*
- *Hyperglycaemia.*
- *Tremors.*
- *Seizures.*
- *Hallucinations.*
- *Alopecia*
- *Diarrhoea.*
- *Insulin-dependant diabetes mellitus.*

m-TOR inhibitors

SIROLIMUS:-



- Sirolimus is a macrolideantibiotic.
- Earlier named as Rapamycin.
- It is obtained from Streptomyces Hygroscopicus.
- It acts by inhibiting the activation of T-cells.

Mechanism of action:-

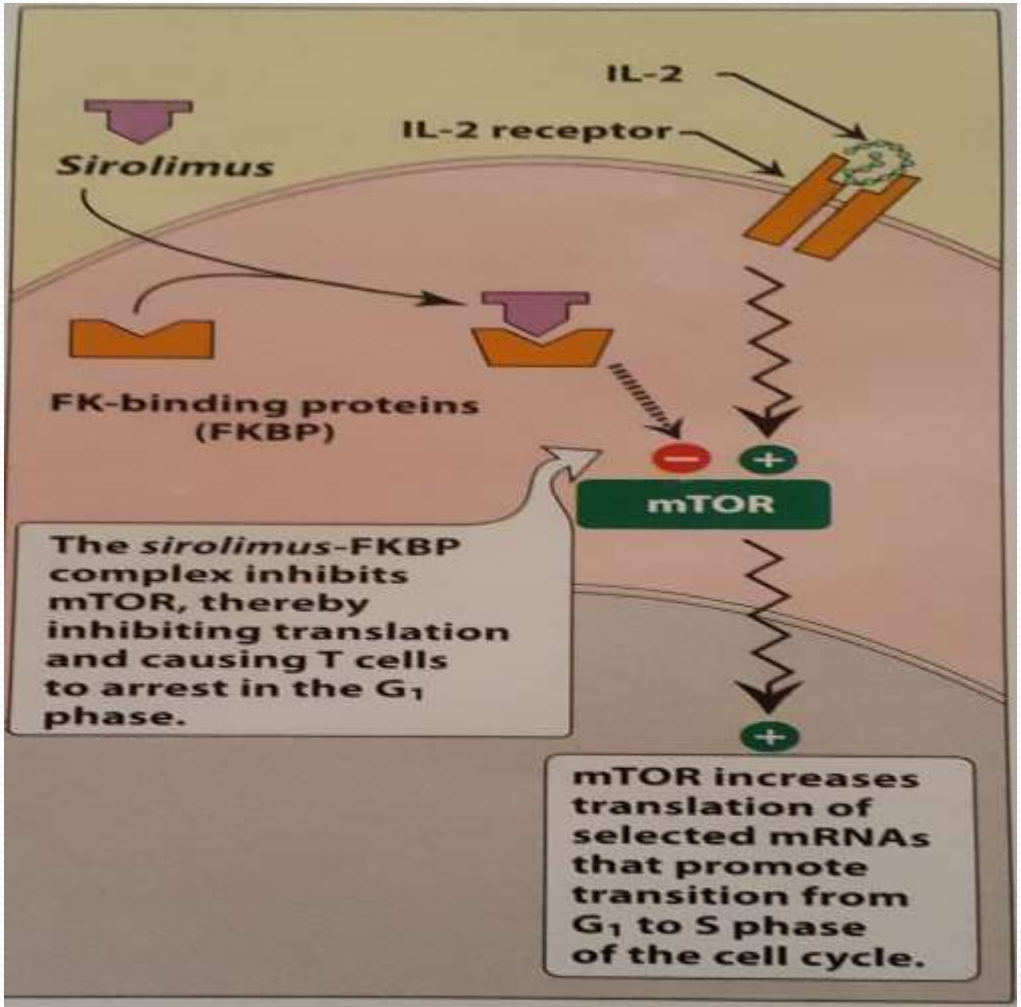


Figure 40.5
Mechanism of action of *sirolimus*. mTOR = molecular target of *rapamycin* (*sirolimus*).

Pharmacokinetics:-

Available only as oral preparation.

- Rapidly absorbed, high fatty meals can decrease the drug's absorption.
- It is extensively bound to plasmaprotein.
- Metabolized by cytochrome P-450 enzyme.
- Plasma half-life ~60hr.
- The parent drug and its metabolite are predominantly eliminated in the faeces.

ADVERSE EFECTs:-

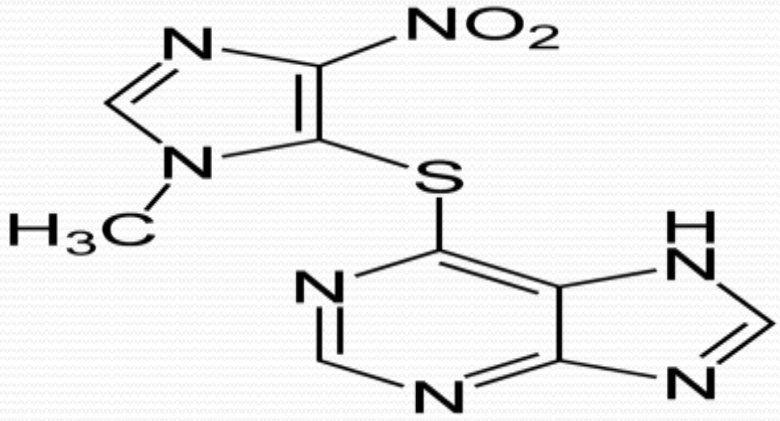
- *Hyperlipidemia*
- *Headache*
- *Nausea*
- *Diarrhoea*
- *Hypertension*
- *Leukopenia*
- *Thrombocytopenia*

Uses:-

- Organ transplantation
- Psoriasis
- Choreoretinitis
- Coronary stents
- Stem cell transplant

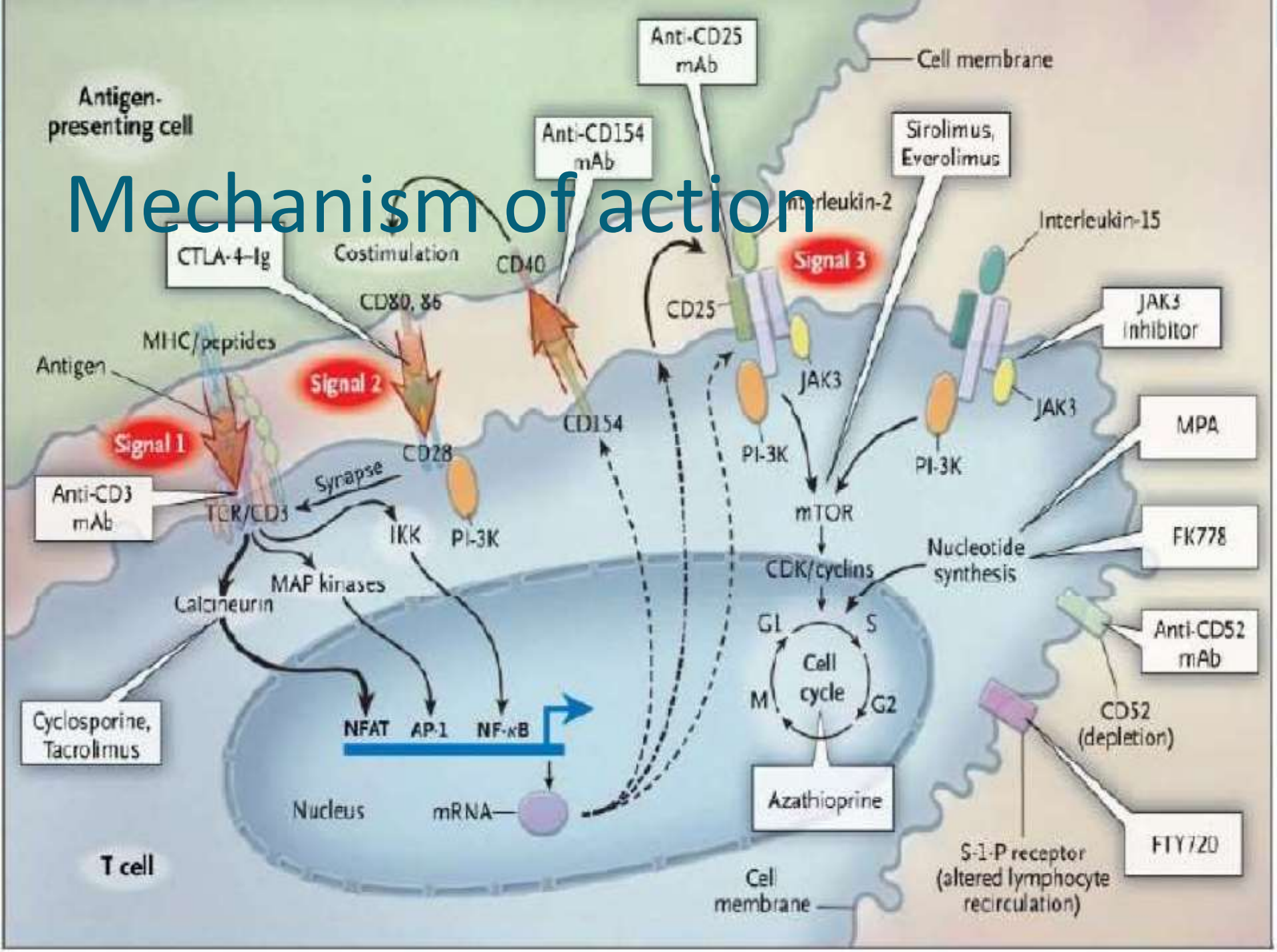
ANTIPROLIFERATIVE DRUGS

AZATHIOPRINE:-



- It is a prodrug of mercaptopurine which is a purine analog.
- It was the first drug to be used for suppression of the immune system after transplantation.

Mechanism of action



Pharmacokinetics:-

- Well absorbed orally.
- Half-life of 5hours.
- Moderately bound to plasma proteins.

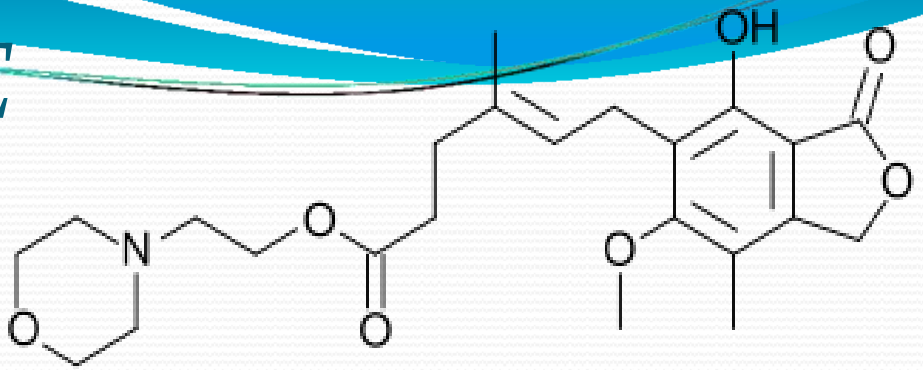
ADVERSE EFECTs:-

- *Bleeding gums.*
- *Chest pain.*
- *Fever or chills.*
- *Painful urination.*
- *Sore throat.*
- *Swollen joints.*
- *Leukopenia.*
- *Bone marrow suppression.*
- *Hepatic dysfunction.*

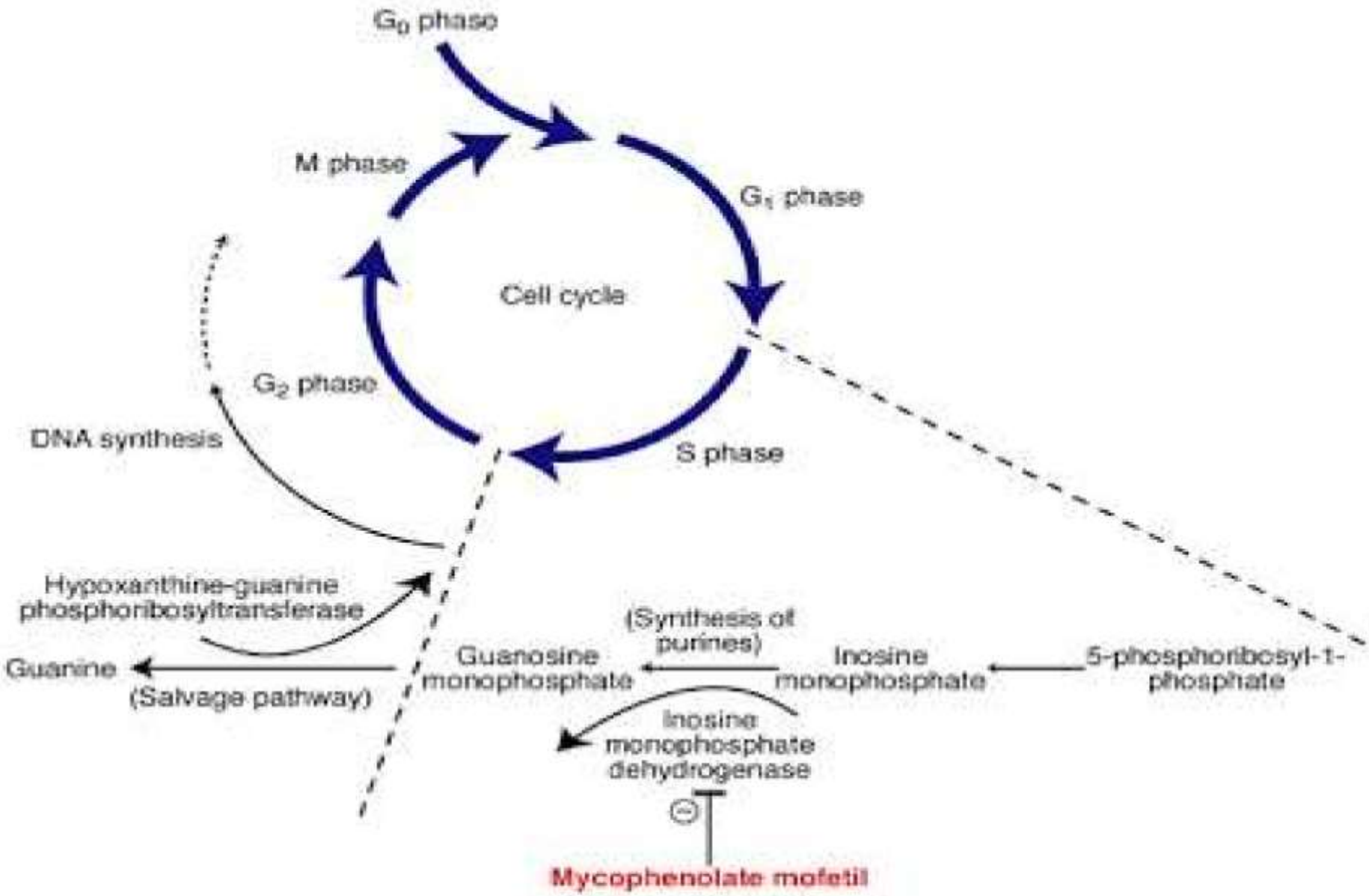
Uses:-

- Prevention kidney transplantation rejection.
- To reduce signs and symptoms of active rheumatoid arthritis.

MYCOPHENOLATE MOFETIL:-



- It is a newer immunosuppressant.
- It is a semi synthetic derivative of mycophenolic acid.
- It is an inhibitor of inosine monophosphate dehydrogenase.



Mechanism of action of mycophenolate mofetil

Pharmacokinetics:-

- Rapidly absorbed orally.
- Half-life is ~16hr

ADVERSE EFECTs:-

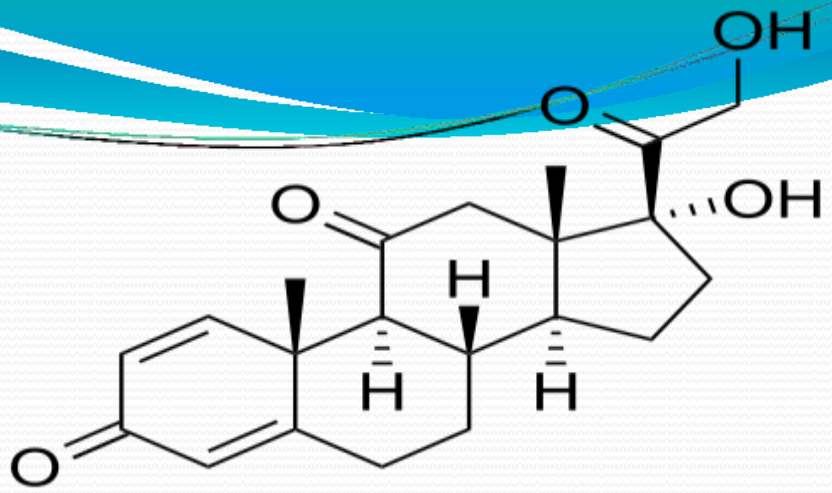
- *Vomiting.*
- *Diarrhoea.*
- *Leucopenia.*
- *Headache.*
- *Gastrointestinal disturbances.*
- *Hypertension.*
- *Bone marrow suppression.*
- *Soft stools.*
- *Anorexia.*

Uses:-

- In treatment of autoimmunedisease.
- In rheumatoid arthritis.
- In treatment of myastheniagravis.
- Psoriasis.
- Autoimmune hemolyticanaemia.
- Inflammatory bowel disease.
- Kidney transplantation.

GLUCOCORTICOIDS

PREDNISOLONE:-



- Nonspecific anti-inflammatory that interupts multiple steps in immune activation.
- Highly effective for prevention of rejection.
- Many adverse-effects long-term.

ADVERSE EFECTs:-

- Weight gain,
- Hypertension
- *Hyperlipidemia*
- Osteopenia
- Hyperglycemia
- Poor wound healing
- Myopathy
- Cataracts
- Peptic ulcers

Uses:-

Used in combination with other Immuno-suppressant drugs.

BIOLOGICAL AGENTS

MUROMONAB-CD3(OKT3):-

- It is a murine monoclonal antibody that is synthesized by hybridoma technology.
- It is used in treatment of acute rejection of renal allografts, etc.
- It is used to deplete T-cells from donor bone marrow prior to transplantation.
- Use as second-line agent when cyclosporine and glucocorticoids fail.

MECHANISM OF ACTION:-

- Muromonab-CD3 binds to CD3 antigen which obstructs the approach of MHCII-antigen complex to the T-cell receptor.
- This prevents the participation of T-cell in the immune response.
- The T-cells get rapidly depleted from blood, partly by cytolysis and partly by their migration to non-lymphoid organs.
- T-cells usually return to normal within 48hrs of discontinuation of therapy.

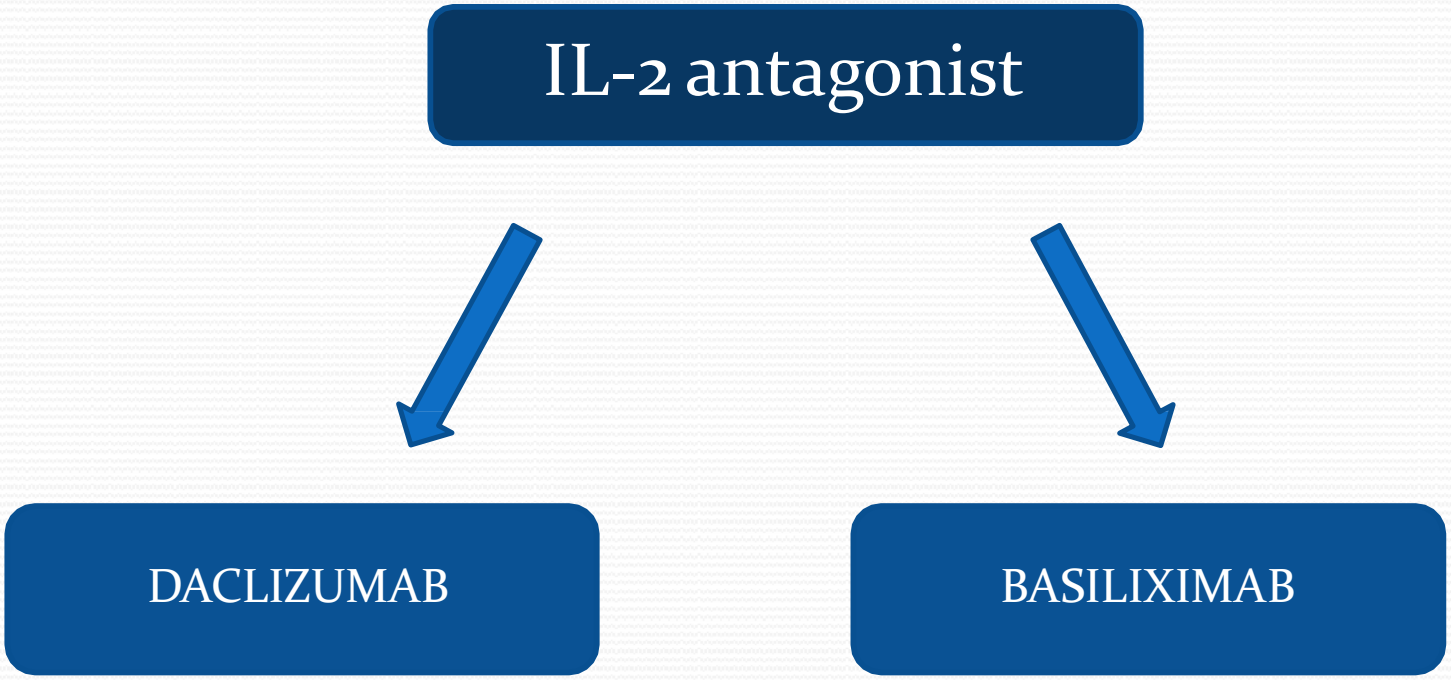
Pharmacokinetics:-

- The antibody is administered intravenously.
- The antibody is extensively metabolized and predominantly excreted in the bile.

ADVERSE EFECTs:-

- *Anaphylactoid reactions.*
- *High fever, chills, wheezing, malaise.*
- *Seizures.*
- *Encephalopathy.*
- *Cerebral edema.*
- *Aseptic meningitis.*
- *Headache.*

INTERLEUKIN-2 RECEPTOR antagonist:-



- Both agents have been approved for prophylaxis of acute rejection in renal transplantation.

MECHANISM OF ACTION:-

- Both Daclizumab and Basiliximab areanti-CD25 antibodies.
- Both bind to the α-chain of the interleukin-2 receptor on the activated T-cells and interfere with the proliferation of the T-cells.
- Basiliximab is ten-fold more potent than daclizumab.
- Blockade of the IL-2 receptor foils the ability of any antigenic stimulus to activate the T-cell response system.

Pharmacokinetics:-

- Both the antibodies aregiven intravenously.
- DACLIZUMAB:-
  - Serum half-life is about 20 days.
  - Blockade of the receptor is 120 days.
- BASILIXIMAB:-
  - Serum half-life is about 7 days.

ADVERSE EFECTs:-

- *Gastrointestinal disorders.*

Standard Regimens

- *Tac/Steroid/MMF or MPA (49%)*
- *Cyclosporin/Steroid/MMF or MPA (28.5%)*
- *Tac/MMF or MPA (3.8%)*
- *Tac/Steroid (1.9%)*
- *Steroid/MMF or MPA (0.9%)*
- *Tac alone (0.6%)*